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Gonadotrophins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure: a randomized, two-by-two factorial trial.

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SUMMARY

Background:

Clomiphene citrate (CC) is in many countries the treatment of first choice in women with normogonadotropic anovulation. If these women ovulate but do not conceive after several cycles with CC, medication is usually switched to gonadotrophins, with or without intrauterine insemination (IUI). We aimed to assess whether switching to gonadotrophins is more effective than continuing CC, and whether IUI is more effective than intercourse.

Methods:

We performed a two-by-two factorial multicenter randomized clinical trial including women with normogonadotropic anovulation not pregnant after six ovulatory cycles with CC (NTR1449). Women were randomized using a central password protected internet-based randomization program to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI or six cycles with CC plus intercourse. CC dosages varied from 50 to 150 mg daily orally and gonadotrophin starting dose was 50 or 75 IU daily subcutaneously.

Primary outcome was conception leading to live birth within eight months after randomization. Primary analysis was by intention to treat. We made two comparisons, one in which gonadotrophins was compared to CC and one in which IUI was compared to intercourse.

Findings:

Between December 8th 2008 and December 16th 2015 we randomized 666 women to gonadotrophins/IUI (N=166), gonadotrophins/intercourse (N=165), CC/IUI (N=163), or CC/intercourse (N=172).

Women allocated to gonadotrophins had more live births than those allocated to CC (167 of 327 women [51·5%] vs. 138 of 334 [41·3%], (RR 1·24 (95% CI 1·05-1·46), p = 0·0124). Addition of IUI did not increase

live births compared to intercourse (161 of 327 women [49·2%] vs. 144 of 334 [43·1%], RR 1·14 (95% CI 0·97-1·35), p = 0·1152).

Multiple pregnancy rates for the two comparisons were low and not different.

There were three adverse events: one child with congenital abnormalities, one immature delivery due to cervical insufficiency, and one stillbirth.

Interpretation: In women with normogonadotropic anovulation and CC failure, a switch of treatment to gonadotrophins increases chances of live birth over treatment with CC, while we could not prove that addition of IUI does so.

Funding: This trial was funded by the Netherlands Organization for Health Research and Development. (80-82310-97-12067).

Key words: ovulation induction, anovulation, clomiphene citrate (failure), gonadotrophins, IUI, PCOS

Research in context panel

Evidence before this study

A comprehensive literature search using PubMed was done on September 15th 2008 before the trial started to identify all previous studies investigating women with clomiphene failure. Search terms included ''ovulation induction'', ''polycystic ovary syndrome'', ''clomiphene citrate'' (CC), '' gonadotrophins'', and ''IUI''. We only identified non-randomized studies indicating that continued treatment with CC and a treatment switch to gonadotrophins are both effective options for these women. If IUI increases pregnancy rates in women with CC failure is unknown.

We wanted to investigate if, in women who have failed to conceive after six ovulatory cycles with CC, ovulation induction with gonadotrophins leads to more live birth rates than continued ovulation induction with CC and if IUI gives more live births than intercourse.

Added value of this study

The M-OVIN (Modified ovulation induction) study compared in anovulatory women with CC failure two types of medication as well as addition of IUI with intercourse. We found that a switch to gonadotrophins significantly increases the live birth rate as compared to continued treatment with CC and that the addition of IUI to gonadotrophins or CC seems not to increase live birth rates in women who are anovulatory.

Implications of all the available evidence

Our findings imply that, for normogonadotropic anovulatory women with CC failure who wish to conceive, continued treatment with CC or a treatment switch to gonadotrophins are both effective options in terms of live birth rates whereas we could not prove this for IUI. The choice between CC and gonadotrophins should be made based on women's preferences, costs and, reimbursement. Considering recent randomized research suggesting that letrozole gives higher live birth rates than CC in the first six cycles, we suggest that future research establishes if continuing letrozole is also effective and safe if women have not conceived within the first six months of treatment.

INTRODUCTION

Women with normogonadotropic anovulation have absent or irregular ovulation due to hypothalamic-pituitary-ovarian dysfunction associated with normal levels of endogenous estradiol.[1] In these women wishing to conceive, Clomiphene Citrate (CC) has long been used as a first-line ovulation induction agent.[2,3] Systematic reviews and meta-analyses show that CC is an effective primary treatment option in therapy-naive women with normogonadotropic anovulation and polycystic ovary syndrome (PCOS).[4-6] Although ovulation is restored in ~75% of women starting ovulation induction with CC, six months of treatment leads to conception in only about half of these women.[5,7] Women not conceiving after six ovulatory cycles are defined as having CC failure.[8] The National Institute for Health and Care Excellence (NICE) guideline recommends not to extend treatment with CC for more than six cycles, but this recommendation is not underpinned by any evidence.[9] In daily practice, these women usually switch to ovulation induction with gonadotrophins and intra-uterine insemination (IUI) is often initiated instead of relying on regular intercourse.[10] However, the effectiveness of a switch to gonadotrophins and IUI compared to continued treatment with CC has never been studied in randomized clinical trials.

We therefore conducted a randomized clinical trial to compare, in women who had six ovulatory cycles with CC but did not conceive, the effectiveness of a switch to gonadotrophins as compared to continued treatment with CC and the effectiveness of adding IUI to either CC or gonadotrophins.

METHODS

Study design

The M-OVIN (Modified ovulation induction) study was a multicenter randomized clinical trial performed in 48 Dutch hospitals within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (www.studies-obsgyn.nl).

The study was granted approval by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (The Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO), The Netherlands (References P08-40 and Eudract number 2008-006171-73). The board of directors of each of the participating centers approved local execution of the study.

The protocol was published previously[11] and the study is registered in the Netherlands Trial Register (NTR1449). Two major adjustments to the protocol were made: The first, in April 2014, regarded a change in the primary outcome from 'ongoing pregnancy' to 'live birth'. The second regarded the sample size which is specified in addendum 2. Both adjustments were approved by the Medical Ethical Committee.

Randomization and masking

Eligible women were informed about the study in or immediately after their sixth treatment cycle either by their doctor or by a dedicated research nurse. After written informed consent women were randomized using a central password protected internet-based randomization program. The randomization list had been prepared by an independent statistician with a variable block size with a maximum block size of 8. There was no masking.

We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing CC and IUI versus intercourse. Women were randomly

assigned to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI, or six cycles with CC plus intercourse.

Study population

Subfertile women ≥ 18 years with WHO type II anovulation (menstrual cycle > 35 days, normogonadotropic, normo-oestrogenic, oligo-anovulation or anovulation), who had been ovulatory for six cycles on CC treatment, with a maximum of 150 mg daily for five days, but who had not conceived, were eligible for the trial. Presence of ovulation was assessed by a basal temperature curve, midluteal progesterone (> 16 nmol/l), detection of a urinary Luteinizing Hormone (LH) surge or transvaginal sonography, depending on the local protocol. All women had undergone a basic fertility work-up including a semen analysis and endocrinological screening to rule out hyperprolactinemia and uncorrected thyroid dysfunction. Couples with male subfertility could not participate. Women with abnormal prolactin (0·05-0·80 IU/l) or thyroid-stimulating hormone (0·4-4·0 mU/l) were also not eligible. Tubal pathology had to be ruled out by either a negative Chlamydia antibody titer (CAT) or hysterosalpingography, transvaginal hydrolaparoscopy, or diagnostic laparoscopy showing at least one patent Fallopian tube. Women with side effects in previous CC cycles were also not eligible.

Interventions

In women allocated to ovulation induction with gonadotrophins, a transvaginal ultrasound was usually performed on the third day of a menstrual bleeding and medication was started on that same day, but women were allowed to start medication up to day five . Treatment was not started if ultrasound showed ovarian cysts >25 mm in mean diameter. According to local protocol, urinary or recombinant gonadotrophins were used with a starting dose of 50 or 75 IU daily. Follicular growth was strictly

monitored by transvaginal ultrasound and we aimed for mono-follicular growth. If ≥ four dominant follicles (≥18 mm) developed, the cycle was cancelled i.e. couples were advised not to have intercourse and the planned IUI was not performed. When at least one follicle with a diameter of ≥ 16 mm was present, ovulation was triggered with 5.000 IU or 10.000 IU of human chorionic gonadotrophin (hCG).

In women allocated to ovulation induction with CC started on the third to fifth day of a menstrual bleeding, in the same dosage as used in the last ovulatory cycle, varying between 50 mg and 150 mg daily, for five days. Ovulation was monitored by a basal temperature curve, midluteal progesterone (> 16nmol/l), a urinary LH surge or transvaginal ultrasound, depending on the local protocol. The women undergoing ovulation induction with CC with IUI underwent monitoring by ultrasound, the other women were usually monitored by basal temperature curve, mid luteal progesterone measurement or urinary LH surge. In case of ovulation not followed by pregnancy, women continued taking the same dose of CC until pregnancy occurred, or until the end of the study eight months after randomization. If ovulation did not occur, the dosage was increased in increments of 50 mg to maximum of 150 mg daily in the next cycles.

In couples allocated to IUI, semen samples were processed within one hour of ejaculation according to the local protocol and women were inseminated 36 to 40 hours after hCG injection. IUI was performed once per cycle.

Follow up

Follow-up started at the day of randomization and ended on the first day of the last menstruation before a positive pregnancy test within six treatment cycles or at eight months after randomization, whatever came first. If pregnant, women underwent an ultrasound at 7 and 11 weeks of gestation and were

followed to delivery of their baby. If they miscarried or had an ectopic pregnancy within eight months after randomization, couples were advised to continue their allocated treatment.

Data were collected by trained research nurses and doctors. They used a structured case record form (CRF) to register the actual interventions, the reproductive outcomes, the occurrence of gestational diabetes, hypertensive disorders, stillbirths, preterm labour, and fetal birth weight as well as the course and outcome of subsequent pregnancies. If the women's medical records did not suffice in giving the necessary information, women were contacted by telephone to ask about their outcomes.

Withdrawal of individual patients

We expected not all couples to complete the eight months of treatment as drop-outs represent normal patient flow, particularly in this protocol in which they already had six ovulatory treatment cycles before inclusion. Women who dropped out of the study were managed according to their preferences.

Outcome measures

The primary outcome measure was conception leading to live birth within eight months after randomization defined as any baby born alive after a gestational age beyond 24 weeks. Secondary outcome measures were ongoing pregnancy, multiple pregnancy, miscarriage (defined as loss of an intrauterine pregnancy confirmed by ultrasound or histological examination before the 20th week of pregnancy), ectopic pregnancy, time from randomization to the birth of a live child, fetal birth weight and pregnancy complications i.e. hypertensive disorders, gestational diabetes and preterm labour.[11] We did not monitor adverse drug events as these are already widely known for both types of medication.

We do not report on all outcomes mentioned in the statistical analysis plan (addendum 3) here. Outcomes like clinical pregnancy rate, ovulation rate and gestational age will be reported elsewhere.

Sample size calculation

When we first planned our study, we designed the trial as a two-by-two2 factorial superiority trial. After recruiting 136 women, we received governmental funding that allowed enlargement of our trial. To evaluate if either switching to ovulation induction with gonadotrophins or addition of IUI would increase the live birth rate from 40% to 55%,[12,13] we needed to include 600 women (alpha of 5% and a power of 88% at three degrees of freedom). We decided to include a total of 660 women since 10% of women became pregnant after randomization but before starting the trial. With these 660 women we would have sufficient power to find a difference in live birth rate for the two comparisons that we have made. A detailed description of all steps in establishing the sample size is provided in addendum 2. A statistical analysis plan (addendum 3) was established prior to data lock.

Statistical analysis

The primary analysis was on an intention to treat basis. For the live birth rates and other binary outcome measures, we calculated absolute risks, relative risks and 95% confidence intervals. Chi-square test statistics were used to assess statistical significance.

We reported categorical data as absolute numbers and percentages. We summarized normally distributed continuous variables as means with standard deviations, and non-normally distributed

continuous variables as medians with interquartile ranges. We formally tested for interaction between the two comparisons.

We constructed Kaplan-Meier curves for time to conception leading to live birth for gonadotrophins versus CC, for IUI versus intercourse and for all four treatment arms separately. They were compared with a log-rank test. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

We assessed whether there was interaction between treatment effect and Body Mass Index (BMI) at cut-off at 25kg/m^2 as this was the mean BMI of our population.

We also performed a per protocol analysis in which we only included women that were treated according to the predefined protocol. SPSS software (version 23.0; IBM Corp., USA) was used for statistical analysis.

Study oversight and role of the funding source

This trial was partially funded by the Netherlands Organization for Health Research and Development (ZonMw). (Health Care Efficiency Research; projectnumber : 80-82310-97-12067). The funder had no involvement in data collection, analysis or interpretation, and had no role in the writing of this manuscript or the decision to submit for publication. The corresponding author confirms to have had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between December 8th 2008 and December 16th 2015, we randomized 666 women. 166 women were allocated to ovulation induction with gonadotrophins combined with IUI, 165 to ovulation induction with gonadotrophins, 163 to ovulation induction with CC combined with IUI, and 172 to continued ovulation

induction with CC (Fig I). We excluded five women from analysis since they were randomized despite not fulfilling the inclusion criteria. None of these women became pregnant. The baseline characteristics were comparable across the four groups (Table I).

Women allocated to gonadotrophins with IUI underwent 540 cycles, women allocated to gonadotrophins underwent 570 cycles, women allocated to CC with IUI underwent 612 cycles and women allocated to CC underwent 681 cycles. Of these cycles respectively 65 (12%) and 61 (11%) were cancelled in the gonadotrophins with IUI and gonadotrophins only arm. Of these cancelled cycles 35 (28%) were due to anovulation, the other cycles were cancelled because of multiple follicular growth. (Table II).

Outcomes

Women allocated to gonadotrophins had significantly more live births than women allocated to CC (167 of 327 women [51·5%] vs. 138 of 334 [41·3%], (RR 1·24 (95% CI 1·05-1·46), p = 0·0124), absolute difference 10·2% (95% CI 2·4-17·9) Table III)). The mean time to conception leading to a live birth was 5 months (95% CI 4·7-5·4) following gonadotrophins and 5·5 months (95% CI 5·1-5·8) following CC (log rank test, p=0·028, Fig II)). There were seven women (2%) allocated to gonadotrophins who conceived a twin pregnancy versus eight women (2%) allocated to CC (RR 0·89 (95% CI 0·33-2·4), p = 0.8262), absolute difference 0%).

Women allocated to IUI had more live births than women allocated to intercourse, but this difference was not statistically different (161 of 327 women [49·2%] vs. 144 of 334 [43·1%], RR 1·14 (95% CI 0·97-1·35), p = 0·1152), absolute difference 6·1% (95% CI -1·71 - 13·8) Table III). The mean time to conception leading to a live birth was 5·2 months (95% CI 4·8-5·5) with IUI and 5·3 months (95% CI 5·0-5·7) with intercourse (log rank test, p=0·27) Fig II)).There were 11 twin pregnancies after IUI (3%) and four after intercourse (1%) (RR 2·8 (95% CI 0·90-8·7), p = 0·0743), absolute difference 2·0%). There were no high order pregnancies.

The number of miscarriages was higher after treatment with gonadotrophins (n=24, 7%) than after CC (n=11, 3%) (RR 2·2 (95% CI 1·11-4·5), p = 0·0243), absolute difference 4·0%). Ectopic pregnancies were comparable between all groups. We found no differences in mean birth weights and pregnancy complications (Table III).

No interaction was seen between the two comparisons (p = 0·932). Also, there was no interaction of BMI and treatment effect for both comparisons.

We included 563 women in the per protocol analysis. We found more live births after gonadotrophins compared to CC: 123/279 women (44·1%) after gonadotrophins versus 90/284 (31·6%) after CC (RR 1·38 (95% CI 1·11-1·72), p = 0·0027), absolute difference 12·5%). Addition of IUI did not increase live births compared to intercourse: 113/277 women (40·8%) after IUI versus 100/286 (35·0%) women after intercourse (RR 1·17 (95% CI 0·94-1·44), p = 0·1548), absolute difference 12·5%).

There were three adverse events: one woman treated with CC conceived a child with congenital abnormalities resulting in second trimester pregnancy termination, one woman treated with gonadotrophins with IUI delivered at a gestational age of 20 weeks due to cervical insufficiency, and one woman treated with CC suffered a stillbirth at a gestational age of 19 weeks.

Table I. Baseline characteristics of the participating couples*

	Gonadotrophins + IUI n = 164	**Gonadotrophins n = 163**	**CC + IUI n = 163**	**CC n = 171**
Mean female age (years)	29·5 ± 3·7	29·9 ± 3·7	30·0 ± 3·6	29·9 ± 4·0
Ethnicity				
Caucasian	131 (85)	134 (88)	133 (86)	141 (89)
Non-Caucasian	24 (15)	18 (12)	21 (14)	18 (11)
Mean BMI **	25·4 ± 5·1	25·6 ± 5·6	25·0 ± 4·9	25·4 ± 5·0
BMI >25.0	76 (46)	81 (49)	64 (39)	81 (47)
Current smoking status	29 (18)	20 (12)	22 (13)	22 (13)
Diagnosis diabetes	1	1	3	2
Previous live birth	32 (20)	35 (21)	36 (22)	34 (20)
Mean duration of subfertility (months)	26·3 ± 14·9	24·5 ± 12·5	24·5 ± 15·5	25·9 ± 19·0
Cycle pattern prior to treatment #				
Amenorrhea	124 (76)	125 (77)	115 (71)	120 (70)
Oligomenorrhea	21 (13)	25 (15)	27 (16)	32 (19)
Unknown	19 (11)	13 (8)	21 (13)	19 (11)
Median TMC *10^6	52 (20-106)	43 (16-113)	53 (15-132)	38 (16-99)
Polycystic ovaries on ultrasound ##	110 (67)	103 (63)	109 (67)	117 (68)
Mean serum biochemical values				
FSH (IU/L)	5·7 ± 2·1	5·7 ± 1·7	6·2 ± 2·2	6·0 ± 2·2
LH (IU/L)	9·7 ± 7·4	10·6 ± 7·8	10·6 ± 7·6	10·9 ± 10·8
Estrogen (pmol/L)	255 ± 295	239 ± 217	201 ± 159	271 ± 460
Total testosterone (nmol/L)	1·6 ± 1·7	1·6 ± 2·0	1·8 ± 2·2	1·8 ± 1·8

* Data are n (%), mean (SD) or median (IQR). There were no significant differences (P<0.05) between the four groups in any of the baseline characteristics.

**BMI = the body-mass index which is the weight in kilograms divided by the square of height in meter. BMI was missing for 24 women; data were imputed by using multiple imputation.

amenorrhea: absence of menstrual bleeding for >6 months. Oligomenorrhea: irregular menstrual bleedings with intervals of >35 days but ≤6 months

Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter

IUI = intrauterine insemination

CC = clomiphene citrate

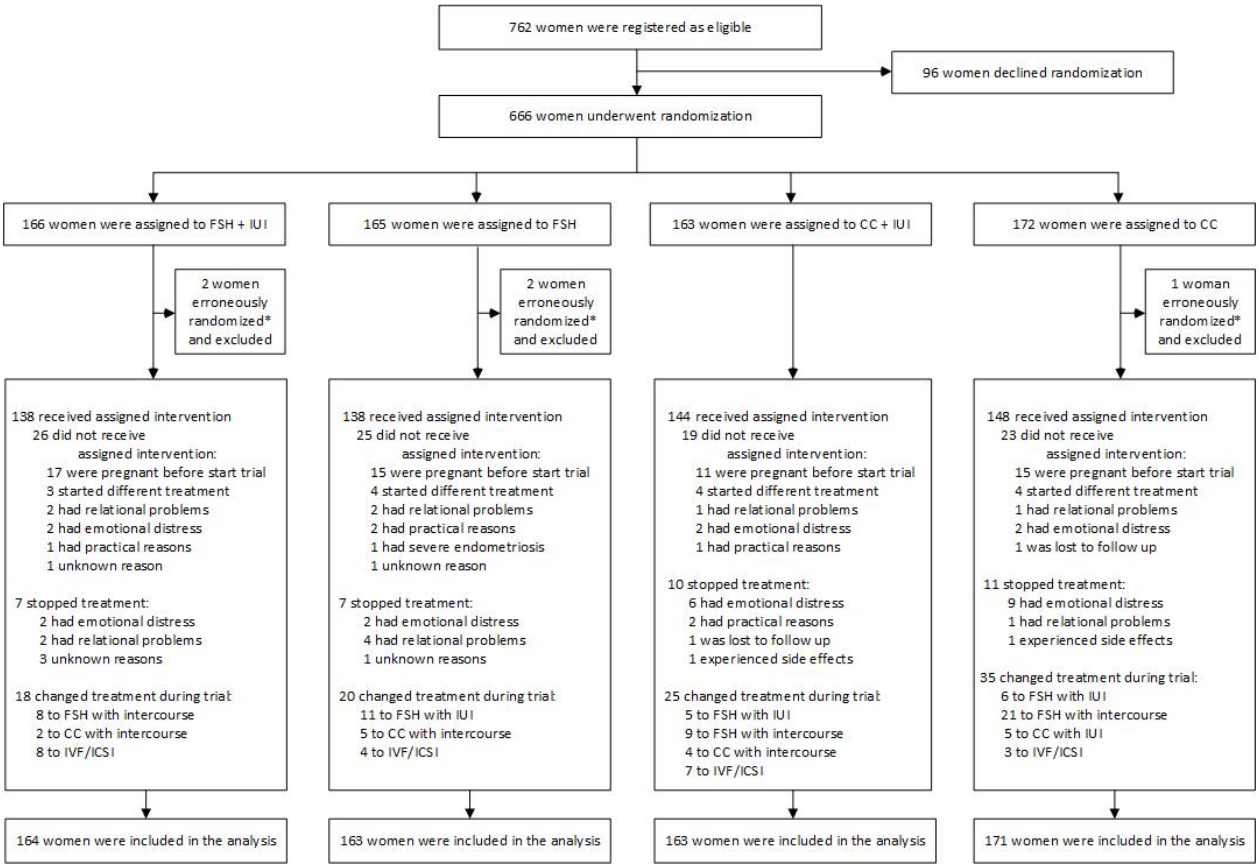
CAT = chlamydia antibody test

TMC = total motile sperm count

FSH = follicle stimulating hormone

LH = luteinizing hormone

Figure I. Study flow chart (Fig 1 has been uploaded in its original format)



FSH = Follicle stimulating hormone = gonadotrophins
CC = clomiphene citrate
IUI = intrauterine insemination
*2 women had thyroid disease, 1 woman had bilateral tubal pathology, 1 male partner had azoospermia, 1 woman only had 2 cycles with CC before randomization

Table II. Cycle results*

	Gonadotrophins + IUI n=164	**Gonadotrophins n=163**	**CC + IUI n=163**	**CC n=171**
Total nr of cycles	540	570	612	681
Mean nr of cycles per woman	3·3 ± 2·0	3·5 ± 2·1	3·8 ± 1·8	4·0 ± 1·9
Mean nr of IUIs per woman	3·2 ± 2·2	0·04 ± 0·3	3·5 ± 2·2	0·05 ± 0·4
Total nr of cancelled cycles	65 (12)	61 (11)	4**	2**
Total units of gonadotrophins per woman	2594 ± 2439	2640 ± 2577	153 ± 823**	223 ± 823**
Total mg of CC per woman	4·5 ± 43·4 #	18·2 ± 128 #	1401 ± 1152	1255 ± 1139

* Data are n (%) or mean (SD)
**After switching to gonadotrophins
# After switching to CC
CC = clomiphene citrate
IUI = intrauterine insemination

Table III. Primary and secondary outcomes*

	Gonadotrophins + IUI n = 164	Gonadotrophins n = 163	CC + IUI n = 163	CC n = 171	Gonadotrophins vs CC RR (95% CI)	Gonadotrophins vs CC P value	IUI vs i RR
Live birth	89 (54·3)	78 (47·9)	72 (44·2)	66 (38·6)	1·24 (1·05-1·46)	0·0124	1·1
Ongoing pregnancy	90 (54·9)	80 (49·1)	72 (44·2)	66 (38·6)	1·26 (1·07-1·48)	0·0063	1·1
Multiple pregnancy** per woman	4 (2·4)	3 (1·8)	7 (4·3)	1 (0·6)	0·89 (0·33-2·4)	0·82	2·8
Miscarriages per woman	15 (9·1)	9 (5·5)	8 (4·9)	3 (1·8)	2·2 (1·11-4·5)	0·02	1·9
Ectopic pregnancy per woman	1 (0·6)	1 (0·6)	3 (1·8)	1 (0·6)	#		#
Mean birth weight (g)	3279 ± 695	3302 ± 769	3178 ± 714	3408 ± 491		0·96	
Pregnancy complications							#
• Hypertensive disorders	4 (2)	6 (4)	5 (2)	2 (1)	#		
• Gestational diabetes	3 (2)	5 (3)	3 (2)	3 (2)			
• Preterm labour	6 (4)	2 (1)	0	1 (1)			

*Data are n (%) or mean ± SD

** All multiple pregnancies were twin pregnancies

No RR was calculated as the proportions are low.

IUI Intrauterine insemination

CC clomiphene citrate

Figure II. Time to conception leading to live birth for the comparison gonadotrophins versus CC, and IUI versus intercourse

Fig II was uploaded in separate files.

DISCUSSION

In this multicenter randomized trial, we found that, among normogonadotropic anovulatory women not pregnant after six ovulatory cycles with CC, a switch to gonadotrophins with strict cycle monitoring increased the live birth rate as compared to continued treatment with CC, while we could not prove this for the addition of IUI. All four treatment arms resulted in acceptable pregnancy rates and low complication rates.

A strength of our study is the two-by-two factorial design. This design allowed us to dissect the effect of gonadotrophins and CC and to establish that IUI does not increases the chances of pregnancy compared to intercourse, although there was a tendency towards higher live birth rates after the fourth IUI-cycle. The per protocol analysis limited to women that received the allocated treatment did not alter these results suggesting that the treatment switches did not have a large effect on live birth chances. A weakness may be that we allowed participating hospitals to use their local protocols for ovulation induction and IUI. On the other hand, this pragmatic approach might increase the generalizability of the results. Plausible biological explanations for the finding of gonadotrophins giving more live births than CC may be the following. First, treatment with gonadotrophins requires strict cycle monitoring whereas treatment with CC does not. Therefore, women treated with gonadotrophins have more specific knowledge on the timing of their ovulation which may lead to a better timing of their intercourse. Second, CC is supposed to have negative effects on the endometrium, but studies examining this effect in relation to pregnancy rates show conflicting results [14-16]. Third, CC possibly induces cervical factor subfertility by influencing the cervical mucus.[17-19]

We do not know whether the differential monitoring in the women that underwent ovulation induction with CC has had impact on the outcomes, but it is not something we expect. The addition of IUI where monitoring was more strict did not result in significantly higher pregnancy chances. We believe one of

the merits of our study is that even with minimal monitoring good results can be obtained with continued ovulation induction with CC.

We found a small, not statistically significant effect of IUI on live birth rates which seemed to increase after cycle four. Apparently, IUI does not contribute to pregnancy chances in women with anovulatory subfertility but, once the ovulation disorder has been resolved by either gonadotropins or CC and conception does not occur, IUI may make a difference. These women could be considered to have unexplained subfertility in whom IUI is standard treatment.

We found 4% multiple pregnancies after gonadotrophins versus 6% after CC which can be explained by the very purpose of ovulation induction in women with anovulation which is to induce mono-follicular growth with low doses of gonadotrophins. [9,11]

There has traditionally there been reluctance in continuing treatment with CC because of safety issues.[9] Of note, direct evidence that cancer risks are increased after six cycles of CC is lacking.

Women treated with gonadotrophins had more miscarriages than women treated with CC. Our study was not powered to detect a difference in miscarriage rate, hence this finding needs to be confirmed in future studies. We found only one second trimester miscarriage in the whole study population, which is very low and in contrast to the miscarriage rate seen after IVF in a fresh transfer cycle in women with PCOS.[20] This is probably due to the fact that ovulation induction aims folliculogenesis of one follicle contrast to superovulation in IVF, resulting in a thinner endometrium in ovulation induction. .

The cumulative live birth rate after CC in cycles 7 to 12 is comparable with a previous observational study.[21] Similarly, the cumulative live birth rate after gonadotrophins is in line with a previous prospective cohort study.[8] This underpins the reliability of our results.

Recent randomized trials and network meta-analyses reported letrozole to be superior to CC in establishing live births.[6,22] We therefore suggest that future research establishes if letrozole is also effective and safe if women have not conceived within the first six months of treatment. Based on our current finding that continued treatment with CC is effective, one might hypothesize even higher live birth rates for continued treatment with letrozole. We therefore suggest to evaluate letrozole in similar settings.

Our results can be used by couples treated with first line ovulatory drugs who weigh the pros and cons of switching to gonadotrophins and addition of IUI. CC is known to cause more side effects than gonadotrophins, while gonadotrophins imply daily injections combined with ultrasound monitoring of follicular development and are more expensive.[23] A recently performed patient preference study on women with anovulation wishing to conceive showed that just over half of these women chooses treatment with the least medical interference and lowest burden whereas under 50% prefers a treatment with the highest success rates regardless of the burden.[24] We planned a cost-effectiveness analyses which will be reported elsewhere.

Our study shows that subfertile women with anovulation who are treated with CC or gonadotrophins with or without IUI reach acceptable pregnancy rates and low complication rates as they continue to conceive even until their 12th treatment cycle. This means that switching to IVF after six failed ovulation induction cycles is not necessary in contrast to the recommendation of the NICE guideline in unexplained subfertility. The choice between these alternatives should therefore be made based on couples preferences, costs, and reimbursement.

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AUTHORS' ROLES

MJN, JO, PGH, FvdV, BWM and MvW designed the trial. NSW and MJN were the trial coordinators. NSW and MvW performed the statistical analyses. NSW was in charge of drafting the manuscript. PGH, FvdV, BWM and MvW participated in the analysis, manuscript drafting and supervision of the work. All authors acquired the data from the participating centers, provided critical discussion and contributed in the preparation of the manuscript.

MvW is corresponding author and confirms to have had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST

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ADDENDUM 1: Trial Protocol

ADDENDUM 2: Sample size calculation

ADDENDUM 3: Statistical analysis plan (SAP)

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